DETAILED ACTION

1. Request for continued examination (RCE) of the application filed on 03/01/2010, is acknowledged. No amendment was made to the claims. Claims 1-61 are pending in the application.

In response to the request, the examiner maintains rejections established in the previous Office action.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. **Claims 1-6, 12, 13, 15-19, 21, 24, 27, 28, 30-32, 38, 39, 40-44, 46, 49, 52-54, 56 and 58-60** are rejected under 35 U.S.C. 102(b) as being anticipated by Rozaklis et al. (Clinical Chemistry, 2002, IDS) (Rozaklis).

Mucopolysaccharidoses (MPS) are a group of metabolic disorders caused by the absence or malfunctioning of lysosomal enzymes needed to break down molecules called glycosaminoglycans - long chains of sugar carbohydrates in each of our cells that help build bone, cartilage, tendons, corneas, skin and connective tissue.

People with a MPS either do not produce enough of one of the 11 enzymes required to break down these sugar chains into simpler molecules, or they produce enzymes that do not work properly. Over time, these glycosaminoglycans collect in the cells, blood and connective tissues. The result is permanent, progressive cellular damage which affects appearance, physical abilities, organ and system functioning, and, in most cases, mental development.

The MPS are part of the lysosomal storage disease family, a group of more than 40 genetic disorders that result when a specific organelle in our body's cells – the lysosome – malfunctions. The lysosome is commonly referred to as the cell's recycling

center because it processes unwanted material into substances that the cell can utilize. Lysosomes break down this unwanted matter via enzymes, highly specialized proteins essential for survival. Lysosomal disorders like MPS are triggered when a particular enzyme exists in too small an amount or is missing altogether.

The biomarkers of MPS, like other lysosomal storage diseases, are oligosaccharides. In this respect, MPS is like all the other disorders of lysosomal storage disease, such as Gaucher disease, Fabry disease, and Pompe disease.

In regard to Claim 1, Rozaklis teaches a method for diagnosing a pre-clinical status, or a clinical status of a lysosomal storage disorders disease in a target patient comprising:

(a) determining a target quantity of a target MPS biomarker (oligosaccharides) from a target biological sample taken from the target patient (see page 132, 134, Table 1-3); and

(b) comparing the target quantity to a reference quantity of a reference MPS biomarker (oligosaccharides) (see page 132, 134, Table 1-3);

wherein,

the target biomarker is the same or equivalent to the reference biomarker, and each of the target MPS biomarker and the reference MPS biomarker is an oligosaccharide (see page 134, Table 1-3);

the reference quantity is determined from a reference human, or group of reference human, having a known clinical status (see Table 1-3);

the target quantity and the reference quantity are determined by a mass spectrometric analysis (see page 134, right col. 4th paragraph); and

a deviation of the target quantity of the target biomarker from the reference quantity of the reference biomarker is a pre-clinical or clinical indication of the disease, an indication of a progression of the disease, or an indication of a regression of the disease (see page 138, left col.).

In regard to Claim 27, Rozaklis teaches a method for diagnosing a preclinical status, or a clinical status, of a lysosomal storage disorders disease in a target animal comprising:

(a) derivatizing a target MPS biomarker (oligosaccharide) with a derivatizing agent (PMP) forming a derivatized target MPS biomarker (PMP-derivatized oligosaccharide) (see page 134, left col. 2nd paragraph);

(b) binding the derivatized target MPS biomarker (PMP-derivatized oligosaccharide) to an extraction compound to give a bound derivatized target MPS biomarker (see page 134, left col. 2nd paragraph);

(c) eluting the bound derivatized target biomarker (derivatized oligosaccharide) from the extraction compound with an elution solution forming an eluted target biomarker (derivatized oligosaccharide) (see page 134, left col. 2nd paragraph;

(d) determining a target quantity of the eluted target biomarker (see page 134, right col.); and

(e) comparing the target quantity with a reference quantity of a reference biomarker (see page 134, right col., Table 1-3);

wherein,

the target biomarker was obtained from a biological sample of a target human having the biomarker contained (see page 132, left col. least paragraph, right col.) therein;

the target biomarker is the same or equivalent to the reference biomarker, and each of the target MPS biomarker and the reference MPS biomarker is an oligosaccharide (see Table 1-3);

the reference quantity is determined in a reference human, or group of reference human having a known clinical status (see Table 1-3); and

a deviation in the quantity of the eluted target biomarker when compared to the reference quantity is a pre-clinical or clinical indication of the disease, a progression of the disease, or a regression of the disease (see page 138, left col.).

In regard to Claims 2 and 28, Rozaklis teaches that the target biological sample or reference biological sample is selected from urine, plasma, or blood (see abstract).

In regard to Claim 3, Rozaklis teaches derivatizing the target biomarker and the reference biomarker with a derivatizing agent prior to determining the quantity of the

target biomarker or the quantity of the reference biomarker (see page 134, left col., right col. 1st paragraph).

In regard to Claims 4 and 30, Rozaklis teaches that the derivatizing agent is 1-phenyl-3-methyl-5-pyrazolone ("PMP") (see page 134, left col., right col. 1st paragraph).

In regard to Claims 5 and 31, Rozaklis teaches that the oligosaccharide comprises a sulfated saccharide molecule having a sugar length ranging from 1 to 12 residues (see Table 1-3).

In regard to Claims 6 and 32, Rozaklis teaches that the oligosaccharide identified from the target biological sample comprises a cleavage product of a glycosaminoglycan ("GAG") (see Table 1-3).

In regard to Claim 12, Rozaklis teaches that the mass spectrometry comprises electrospray-ionization tandem mass spectrometry ("ESI-MSMS") or liquid chromatography tandem mass spectrometry ("LC-MSMS") (see page 134, right col., Figure 4).

In regard to Claims 13 and 39, Rozaklis teaches that the mass spectrometry is carried out in conjunction with HPLC or an immunoassay (see page 132 left col. 2nd paragraph).

In regard to Claims 15-18, 40, 41, 43 and 44, Rozaklis teaches that lysosomal storage disorders can be treated with enzyme-replacement therapy (see page 132, left col. 1st paragraph). Therefore, monitoring and adjusting the treatment of MPS is inherently the function and goal of Rozaklis' method.

In regard to Claims 19, 21, 42 and 46, Rozaklis teaches that the target biological sample and the reference biological sample contain MeLac as an internal standard. MeLac is a non-physiological oligosaccharide that is similar to the oligosaccharide being investigated (see page 137, right col. 3rd paragraph).

In regard to Claims 24 and 49, Rozaklis teaches that the target is an infant (see Table 2).

In regard to Claim 38, Rozaklis teaches that determining the target quantity comprises a mass spectrometric analysis (see page 134, right col.).

In read to Claim 52, Rozaklis teaches a kit (materials) for diagnosing a pre-clinical status, or a clinical status of a lysosomal storage disorders disease in a target animal comprising:

(a) an oligosaccharide derivatization agent (1-phenyl-3-methyl-5-pyrazolone (PMP)) (see page 132, right col. 5th paragraph);

(b) an acid solution (formic acid) (see page 132, right col. 5th paragraph);

© an internal standard (MeLac) (see page 132, right col. 5th paragraph);

(d) a solid phase extraction column (C18 reverse-phase extraction column)(see page 132, right col. 5th paragraph);

(e) a solid phase extraction column wash solution ($CHCl_3$) (see page 132, right col. 5th paragraph); and

(f) an oligosaccharide elution solution (CH_3CN/formic acid) (see page 132, right col. 5th paragraph).

In regard to Claim 53, Rozaklis teaches that the oligosaccharide derivatization agent is a solution comprising: 1-phenyl-3methyl-5-pyazolone (PMP) (see page 134, left col.).

In regard to Claim 54, Rozaklis teaches that the acid solution comprises formic acid (see page 134, left col.).

In regard to Claim 56, Rozaklis teaches that the internal standard comprises a non-physiological oligosaccharide that is similar to the oligosaccharide being investigated (see page 137, right col.).

In regard to Claim 58, Rozaklis teaches that the solid phase extraction column comprises a C18 reverse phase column (see page 134, left col.).

In regard to Claim 59, Rozaklis teaches that the solid phase extraction column wash solution comprises: $CHCl_3$ (see page 134, left col.).

In regard to Claim 60, Rozaklis teaches that the oligosaccharide elution solution comprises: CH_3CN and formic acid (see page 134, left col.).

Claim Rejections – 35 USC § 103

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 22, 47 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis**.**

In regard to Claims 22, 47 and 57, Rozaklis does not specifically teach that the internal standard is the non-physiological oligosaccharide derived from a chondroitinase digestion of chondroitin sulfate having an unsaturated uronic acid at the non-reducing end. The applicant is advised that the Supreme Court recently clarified that a claim can be proved obvious merely by showing that the combination of known elements was obvious to try. In this regard, the Supreme Court explained that, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has a good reason to pursue the known options within his or her technical grasp." An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of the case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. The combination of familiar elements is likely to be obvious when it does no more than yield predictable results. (See *KSR Int'l v. Teleflex Inc.*, 127 Sup. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007)). In that regard, Rozaklis teaches that when suitable labeled isotopes are not readily available for oligosaccharides, one can use a non-physiologic oligosaccharide as an internal standard (see page 137, right col. 3rd paragraph). Therefore, at the time of the invention it would have been obvious to ordinary skill in the art to use non-physiologic oligosaccharide derived from a chondroitinase digested chondroitin sulfate (CS) having an unsaturated uronic acid at the non-reducing end, because this non-physiologic oligosaccharide derived from CS does no more than being an internal standard in mass spectrometry calibration as taught by Rozaklis.

6. Claims 7, 23, 25, 26, 33, 48, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Byers, et al. (Molecular Genetics and Metabolism, 1998, IDS) (Byers).

In regard to Claims 7 and 33, Rozaklis does not explicitly clarify that the GAG is eratin sulfate, dermatan sulfate, eratin sulfate, or chondroitin sulfate. However, the GAG being eratin sulfate, dermatan sulfate, eratin sulfate, or chondroitin sulfate is well known in the art. Byers teaches that the Glycosaminoglycans (GAG) accumulated and excreted in the mucopolysaccharidoses is eratin sulfate, dermatan sulfate, eratin sulfate, or chondroitin sulfate (see page 282, right col. 1st paragraph). At time of the invention, one of ordinary skill in the art would have recognized that the GSG analyzed by Rozaklis is eratin sulfate, dermatan sulfate, eratin sulfate, or chondroitin sulfate based on Byers' teaching.

In regard to Claims 23 and 48, Rozaklis teaches that the MPS disease includes MPS-III, and MPS-VI (see page 132, left col. 2nd paragraph). Byers teaches that MPS includes I, II, IIIA, IIIB, IIIC, IIID, IVA and VI subtypes (see page 282, right col.). At the time of the invention it would have been obvious for ordinary skill in the art to include I, II, IIIA, IIIB, IIIC, IIID, IVA and VI as subtype of MPS as taught by Byrers in Rozaklis' method.

In regard to Claims 25, 26, 50 and 51 Rozaklis does not specifically teach that the target MPS biomarker is contacted with an enzyme that characterizes a particular MPS disease subtype before determining the target quantity. Byers teaches contacting the target MPS biomarker with an enzyme (α-L-iduronidase) that characterizes a particular MPS disease subtype before determining the target quantity (see page 283, right col. last paragraph). Byers derives results by comparing the quantity of GAG analysis before and after the enzyme digestion. At the time of the invention, it would have been obvious to one of ordinary skill in the art to contacting the target MPS biomarker with an enzyme (α-L-iduronidase) that characterizes a particular MPS disease subtype before determining the target quantity as taught by Byers, so that the subtype of MPS can be determined.

7. **Claim 14** is rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Leeuwenburgh et al. (The American Physiological Society, 1999) (Leeuwenburgh).

In regard to Claim 14, Rozaklis does not specifically teach that the target quantity and the reference quantity are normalized to creatinine or another oligosaccharide. Normalizing the quantity of the mass spectrometry result is routinely performed in the art to correct individual differences of the samples. For example, Leeuwenburgh teaches normalizing the result of mass spectrometry to urine level of creatinine to correct individual differences of samples (see page R130, right col. 1st paragraph). At the time of the invention, it would have been obvious to one of ordinary skill in the art to use the urine level of creatinine to normalize the urine level of GAG in MS, so that the individual sample differences an be corrected.

8. **Claims 20, 45 and 55** are rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Hopwood et al. (Biochemical Journal, 1985, IDS) (Hopwood).

In regard to Claims 20, 45 and 55, Rozaklis teaches that using stable-isotope as an internal standard is the best method for accurate quantification of compounds in biological sample in MS analysis (see page 137, 3rd paragraph). Hopwood teaches that GlcNAc6S is found in abnormal amount in the urine of a patient with MPS IIID (see page 229, right col.). Therefore, a deuterated N-acetylglucosamine-6-sulfate ("GlcNAc6S(d3)") will be an obvious choice of internal standard for mass spectrometry analysis in Rozaklis' method.

9. **Claims 8-11 and 34-37** are rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Byers as applied to claims 7, 23, 25, 26, 33 above, and further in view of Merry et al. (The Journal of Biological Chemistry, 1999) (Merry).

In regard to Claims 8-11 and 34-37, Byers teaches that Glycosaminoglycans (GAGs) contains linkages of N-acetylgalactosamine-glucuronic acid (GlcA-GalNAc-) and N-acetylgalactosamine-iduronic acid (IdoA-GalNAc-) (see page 288, left col.). Merry teaches that iduronic acid (IdoA) is the major uronic acid component of the GAGs dermatan sulfate and heparan sulfate (see Figure 2). Therefore, at time of the invention it would have been obvious to one of ordinary skill in the art to recognize that the fragments of dermatan sulfate, eratin sulfate, eratin sulfate and chondroitin sulfate

comprise combination of iduronic acid (IdoA), N-acetylgalactosamine (GalNAc), uronic acid (UA), glucuronic acid (GlcA) and sulfate (S).

10. **Claim 61** is rejected under 35 U.S.C. 103(a) as being unpatentable over Rozaklis in view of Byers, Hopwood, Leeuwenburgh and Merry.

In regard to Claim 61, Rozaklis teaches a method for diagnosing a pre-clinical status, or a clinical status, of a lysosomal storage disorders disease in a target animal comprising:

(a) determining a target quantity of a target MPS biomarker (oligosaccharide) from a target biological sample taken from the target animal (see page 134); and

(b) comparing the target quantity to a reference quantity of a reference MPS biomarker (oligosaccharide) (see Table 1-3);

Rozaklis teaches that the target lysosomal storage disorders biomarker is the same or equivalent to the reference lysosomal storage disorders biomarker (see Table 1-3), and each of the target lysosomal storage disorders biomarker and the reference lysosomal storage disorders biomarker is an oligosaccharide (see page 134),

Rozaklis teaches that the target biomarker and the reference biomarker are derivatized with a derivatizing agent prior to determining the quantity of the target biomarker and the quantity of the reference biomarker, wherein, the derivatizing agent comprises 1-phenyl-3-methyl-5-pyrazolone ("PMP") (see page 134);

Rozaklis teaches that the reference quantity is determined from a reference human, or group of reference human, having a known clinical status (see page 132);

Rozaklis teaches that a deviation of the target quantity from the reference quantity is a pre-clinical or clinical indication of the lysosomal storage disorders disease, an indication of a progression of the lysosomal storage disorders disease, or an indication of a regression of the lysosomal storage disorders disease (see page 138),

Rozaklis teaches that the target quantity and the reference quantity are determined using a mass spectrometry method (see [age 134); and

As has been discussed in regard to claims 8-11 and 34-37, Rozaklis-Byers teaches that oligosaccharide comprises: HNAcS; HNAcS2; HNS-UA; UA-HNAcS; HNAcS-UA; UA-HNAc-UA-S; (HNAc-UA)2-S; (HNAc-UA)2(S)2; or hexasac.

As has been discussed in regard to Claim 14, Rozaklis- Leeuwenburgh teaches normalizing the result of mass spectrometry to urine level of creatinine to correct individual differences of samples (see page R130, right col. 1st paragraph).

As has been discussed in regard to Claims 23 and 48, Rozaklis-Byers teaches that the MPS disease is selected from a group comprises: MPS I, MPS II, MPS IIIA, MPS IIIB, MPS IIIC, MPS IIID, MPS IVA, MPS VI, or multiple sulfatase deficiency;

As has been discussed in regard to Claims 20, 45 and 55, Rozaklis-Hopwood teaches that an internal standard is utilized to accurately determine the target quantity and the reference quantity, wherein the internal standard comprises a deuterated N-acetylglucosamine-6-sulfate ("GlcNAc6S(d3)").

Response to Arguments

11. Applicant's arguments filed 03/01/2010 have been fully considered but they are not persuasive.

The Rozaklis reference was published in January 2002. The effective filing date of the present application in the United States is 06/13/2003. Therefore, the Rozaklis reference is available as a reference against the current application under 35 U.S.C. 102(b), because the reference was published more than one year prior to the date of application for patent in the United States.

Conclusion

This is a continuation of applicant's earlier Application No. 10/517,899. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT XU whose telephone number is (571)270-5560. The examiner can normally be reached on Mon-Thur 7:30am-5:00pm, Fri 7:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571)272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

4/5/2010

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

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